In re Application of: Yoram REITER et al.
Serial No.: 10/510,229
Filed: October 13, 2004
Final Office Action Mailing Date: October 9, 2007

Examiner: Zachariah LUCAS
Group Art Unit: 1648
Attorney Docket: 28429

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 141-160 and 196-211 are in this Application. Claims 150 and 200-211 have been withdrawn from consideration. Claims 141-149, 151-160, and 196-199 have been rejected under 35 U.S.C. §112. Withdrawn claims 150 and 200-211 have been amended herewith. Claims 141, 142, and 197-199 have been amended herewith. Claim 196 has been cancelled herewith. New claim 212 has been added herewith.

A Request for Continued Examination (RCE) is being submitted concurrently.

After amendments, the application now comprises claims 141-160, and 197-212, of which claim 141 is in independent form.

35 U.S.C. §112, Second Paragraph Rejections

The Final Office Action has rejected claims 197 and 198 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Final Office Action states that each of these claims depends from cancelled claim 161, and it is therefore not clear what invention these claims are describing. In addition, the Final Office Action states that for the purposes of this action, the claims are treated as depending from claim 196.

Applicants have amended claims 197 and 198 to depend from claim 142, thereby rendering moot the Office Action's rejection with respect to these claims.

In view of the above claim amendments Applicants believe this 35 U.S.C. §112, second paragraph rejection has been overcome and request that it be withdrawn.

35 U.S.C. §112, First Paragraph Rejections: enablement rejections

The Final Office Action has rejected claims 141-149, 151-160 and 196-199 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for methods of killing cells using the heavy and light chain variable regions of Fab T3F2 as described on Page 72 of the specification, wherein the antibodies comprise

both the antigen-binding region and a functional domain permitting the antibody to kill the target cells, does not reasonably provide enablement for the claimed methods wherein the antibody may be any antibody that meets the functional limitations of claim 141, or a fragment of such an antibody.

The Final Office Action states that this rejection includes two basis of rejection. The first basis of rejection will now be addressed. The Final Office Action has rejected claims 141-149, 151-160 and 196-199 because the teachings of the application and the art indicate that the antigen-binding region alone is insufficient to kill cells and inclusion of certain constant domain sequences to permit targeted cell killing or use of a functional moiety such as a toxin are needed.

While traversing Office Action's rejection and in order to expedite prosecution of this case, Applicants have elected to amend claim 141 rendering explicit what was already implicit and in line with Office Action's tentative suggestion for enabled claim language *i.e.*, the antibody comprising *"a domain allowing the antibody to kill said target cell"*. Dependent claims 142, 197-198 have been amended accordingly. Ample support for the amendments can be found in the instant application as filed, see for example, Pages 13 (lines 8-12), 22 (lines 23-27), 26 (lines 31-33), 27 (lines 1-20), 34 (lines 19-33) and 35 (lines 1-10) and 50 (lines 19-24).

The Office Action states that the second basis of rejection is concerned with the additional claim language of claim 141, which requires that the antibody be capable of binding to a target antigen-presenting molecule (APM)/antigen complex without being capable of binding either of the two (*i.e.*, the APM or the antigen) individually, and that in support of the arguments in traversal against the previously made obviousness rejection, the Applicants amended the claims to insert the additional functional language and provided two declarations and other evidence indicating that the process for obtaining such antibodies is a "difficult task" and that those in the art have been trying and failing to do so for a long time. The Office Action further states that the teachings provided by the Applicants in these declarations indicate that there is a great deal of unpredictability and complexity in the task of identifying antibodies that meet the required functional features, however, the application provides no means

for overcoming the difficulties of the past other than providing a mere brute force method of performing multiple levels of screening on large phage libraries of potential antibodies; that it is noted that while the Applicant did identify a number of antibodies that "purportedly" meet the newly added functional features, the application teaches that the identification of so many antibodies was "unexpectedly high"; that it is not clear that the disclosed antibodies do in fact meet the additional function requirements of not recognizing the APMs or antigens individually (*i.e.*, not as part of the APM/antigen complex); and that the application provides no indication that this method of obtaining antibodies could be repeated with respect to other target antigens. The Office Action's rejections are respectfully traversed.

Applicants point out that in sharp contrast to Office Action's assertion the instant application provides detailed teachings describing how to reproducibly obtain the claimed antibodies such that one of ordinary skill in the art will be able to obtain the claimed antibodies for killing a target human cell expressing or displaying a complex composed of a human antigen-presenting molecule (APM) and an antigen derived from a pathogen (the "APM/antigen complex", hereinafter) and not the individual components of the complex, without undue experimentation.

In the following paragraphs Applicants refer the Examiner to the teachings of the instant application which enable one skilled in the art to obtain the claimed antibodies with the added functional features (paragraphs 1-2, below); further aspects of the rejection are addressed in paragraphs 3-5 (below).

1. Isolation of antibodies capable of binding the APM/antigen complex – The instant specification provides ample support for methods of generating the claimed antibodies, see e.g., Pages 14-16 and 64-77. To simplify issues, Applicants provide herewith a summary of the teachings provided in the aforementioned pages. Thus, soluble, properly folded human APM/antigen complexes are generated by recombinantly expressing the APM molecule in bacteria and *in vitro* re-folding the APM molecule in the presence of restricted antigenic peptides derived from a pathogen (e.g., Tax peptide) [see Page 65 (from line 14) through Page 66 (line 1)]. Phage clones are first screened for binding the APM/antigen complex (Pages 66, 71-

72), and then the specificity of the library-derived antibodies to the complex and not its individual components (when not in complex) is assayed as described below.

2. Screening for antibodies with the required functional features, i.e., being capable of binding the APM/antigen complex but not the APM or the antigen when not in complex – Screening for antibodies with the required functional features is described in detail in the instant specification, see e.g., pages 66-79 of the instant specification. Briefly, to screen for antibodies with the claimed limitations, the following experiments can be performed: (1) the antibodies are contacted with ELISA plates pre-coated with the APM/antigen complexes or with complexes formed of the APM and control peptides and the ability of the antibodies to bind the APM/antigen complex but not the APM when complexed with control peptides (representing the APM in the absence of the antigen of interest) under conditions which ultimately support such binding is recorded (see Page 67, lines 2-17 and Table 1 in the instant application as filed). In addition, the antibodies are contacted with ELISA plates pre-coated with the antigenic peptide alone, under conditions which ultimately support such binding. Failure of the antibodies to bind the antigenic peptide alone as compared to the APM/antigen complex is recorded (see Page 74, lines 25-27 in the instant application as filed); To improve screening (2) flow cytometry analyses are performed using cells which are either expressing or not-expressing (*i.e.*, devoid of) the APM molecule and which are loaded with the specific antigenic peptide or with control peptides. Thus, the ability of the antibodies to bind cells displaying the APM/antigen complex but not cells displaying the APM/control peptide complex or to cells devoid of the APM which are loaded with the specific antigenic peptide is recorded (see Page 68, lines 17-26 and Figures 5a-f, in the instant application as filed). In addition, flow cytometry analyses are performed using similar cells (*i.e.*, cells either expressing or devoid of the APM) which are transfected with an expression vector encoding the target antigen protein and the ability of the antibodies to bind to cells displaying the APM/antigen complex but not to cells expressing the antigen alone is recorded (see Page 68, lines 27-33, Page 69, lines 1-9 in the instant application as filed).

Thus, in view of the above description, it is clear that the instant application teaches how to obtain the claimed antibodies without undue experimentation.

3. Not a "difficult task" - With respect to Office Action's assertion that the teachings provided by the Applicants in the Declarations indicate that there is great deal of unpredictability and complexity in the task of identifying antibodies that meet the required functional features, Applicants point out that the Office Action has misinterpreted the cited declarations. Thus, in sharp contrast to Office Action's assertion the unpredictability and lack of success relate to prior art teachings [see e.g., Declaration of DeLisi (of record), Page 2, from line 20, through Page 4 (first paragraph); Declaration of Cerundolo (of record), Page 2, from line 19, through Page 4 (second paragraph)] and not to the teachings of the instant application (see Declaration of DeLisi, Page 4, lines 4-14; Declaration of Cerundolo Page 4, lines 8-18).

In addition, with respect to Office Action's assertion that the application teaches that the identification of so many antibodies was "unexpectedly high" (Page 71, lines 23-26), Applicants point out that this statement refers to the success of the method of the instant application as compared to the lack of success of prior art methods (e.g., Tumminen et al., or Rubin et al., who failed to identify such antibodies).

4. Antibodies of the instant specification comply with the claimed features – With respect to Office Action's assertion that the specification does not reasonably provide enablement for the claimed methods wherein the antibody may be any antibody that meets the functional limitations of claim 141 and that it is not clear that the disclosed antibodies do in fact meet the additional functional features, Applicants point out that in sharp contrast to Office Action's assertion, the instant specification in fact does report that the disclosed antibodies exhibit the claimed functional features. Thus, as shown in the instant application, antibodies directed against the HLA-A2:$Tax_{11\text{-}19}$ complex (e.g., Fab's T3D4, T3E3 and T3F2) were capable of binding the HLA-A2:$Tax_{11\text{-}19}$ complex but not the HLA-A2 when in complex with other peptides (*i.e.*, representing human antigen-presenting molecule in an absence of the antigen derived from the pathogen, as claimed, see e.g., 10 control peptides derived from viral

epitopes of CMV or EBV, or tumor-associated epitopes such as telomerase, melanoma or MART; See for example, Figures 3a-c; Page 15, lines 6-8, Page 74, lines 11-24 of the instant application as filed) or the Tax_{11-19} peptide alone (See Page 74, lines 25-27 of the instant application as filed). Similarly, the antibodies were capable of binding cells expressing HLA-A2 which were loaded with the Tax_{11-19} peptide but not the same cells when loaded with control peptides (See Figures 5a-f, Page 15, lines 18-27; Page 75, lines 8-33 and Page 76, lines 1-2) or to cells devoid of the APM (not expressing HLA-A2) which were loaded with the antigenic peptides (See Page 75, lines 27-31 in the instant application as filed). In addition, the antibodies of the claimed invention were shown capable of binding cells expressing the HLA-A2 molecule (e.g., JY cells) which were transfected with an expression vector encoding the HTLV-1 Tax protein (Figure 7a), but not cells devoid of the HLA-A2 molecule (e.g., APD cells) which were transfected with the same Tax expression vector [Figure 7b; See also Pages 16 (lines 3-16), 76 (lines 26-33), 77 (lines 1-2) in the instant application as filed]. Altogether, these results demonstrate that the instant application enables antibodies which comply with the functional limitations of claim 141, *i.e.*, which bind the APM/antigen complex and not the APM or the antigen when not in complex.

In addition, Applicants refer the Examiner to MPEP guidelines (2164.02 Working Examples), which state that:

> *"A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled".*

Thus, in view of the teachings of the instant specification, the level of the skilled artisan and the working example, it is Applicants' position that a method of using the claimed antibodies with functional limitations of claim 141 is enabled.

5. The scope of the present claims is enabled – With respect to Office Action's assertion that the claims are lacking adequate support to enable the scope of the presently claimed inventions and that the application provides no indication that

this method of obtaining antibodies could be repeated with respect to other target APM/antigen complexes, Applicants point out that one is not required to specifically enable every conceivable embodiment, but only to teach how to carry out the invention.

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied.

In addition, to demonstrate that the application is enabled as written, Applicants provide herewith experimental results showing that the teachings of the application can be applied to obtain additional antibodies for use in the claimed methods. By applying the disclosed teachings for the selection of antibodies recognizing other target antigens and routinely achieving the predicted result, enablement commensurate with claimed scope is shown.

Attached is a Declaration under 37 C.F.R. §1.132 by Dr. Yoram Reiter, a co-inventor of the instant application, demonstrating. that using the teachings of the instant application (see sections "1" and "2" hereinabove and Pages 64-77 in the instant application), various antibodies directed against other APM/antigen complexes which comply with the claimed functional features have been isolated. In addition, the attached Declaration demonstrates that the application as written enables obtaining the antibodies without failure. Table 1, hereinbelow, summarizes the findings disclosed in the attached Declaration and Appendix.

Table 1
Antibodies which were identified following filing and based on the teachings of the instant application

APM/antigen complex	***Number of antibodies***	***Assay***	***Reference in the instant***

			application for the antibody target (the APM/antigen complex)
MHC class I/CMV peptide (Pages 1-4 in the Attached Appendix)	Two distinct antibodies	1. ELISA assays showed that the antibodies bind the HLA-A2/CMV pp65(495-503) complex but not complexes of the same APM with control peptides such as: HLA-A2/EBV; HLA-A2/hTERT (865); HLA-A2/hTERT (540); or HLA-A2/melanoma gp100 (209); or the antigenic peptide alone (CMV pp65(495-503). 2. FACS analyses showed that the antibodies specifically bind to HLA-A2 positive cells which were loaded with the CMV $pp65_{495-503}$ peptide but not to HLA-A2 positive cells which are loaded with control peptides. In addition, the antibodies did not bind to cells which are devoid of the APM (HLA-A2 negative) and which were loaded with the specific CMV $pp65_{495-503}$ peptide.	HLA-A2 (Page 13, lines 18-19); CMV (Page 74, lines 18-21)
MHC class I/HIV Gag antigenic peptide (Pages 5-7 in the Attached Appendix)	Four distinct antibodies	1. ELISA assays showed that the antibodies bind to the complex of HLA-A2/HIV but not to control complexes such as HLA-A2/h-TERT (540); HLA-A2/MART-1 (209); or HLA-A2/h-TERT (865) or the antigenic peptide alone (HLA-A2/HIV). 2. FACS analyses showed that the Fab antibodies specifically bind to HLA-A2 positive cells which were loaded with the HIV antigenic peptide but not to HLA-A2 positive cells which were loaded with control antigenic peptides. the antibodies were capable of ,In addition positive cells transfetced with 2A-binding HLA positive 2A-GAG gene but not to HLA-the HIV (TAX ,.g.e) ontrol genecells transfected with a c (APD B cells) negative cells 2A-or to HLA GAG-which were transfected with the HIV .gene	HLA-A2 (Page 13, lines 18-19); HIV (Page 39, line 33, through Page 40, line 1)
MHC class I/influenza M1 peptide (Pages 7-8 in the Attached Appendix)	10 distinct antibodies	1. ELISA assays showed that the antibodies bind to the complex of HLA-A2/Influenza M1 peptide but not to a control complex (e.g., HLA-A2/h-TERT (540)	HLA-A2 (Page 13, lines 18-19); Influenza (Page 64, line 22)

		2. FACS analyses showed that the antibodies specifically bind to HLA-A2 positive cells which were loaded with influenza M1 peptide but not to HLA-A2 positive cells which are loaded with control peptides.	

Thus, the experimental results described herewith and the attached Declaration demonstrate that the application is enabled as written for the full breadth of the claims.

In the absence of adequate reasons advanced by the Office Action to establish an enablement rejection, Applicants hereby request withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph.

35 U.S.C. §112, First Paragraph Rejections: written description rejections

The Office Action has previously rejected claim 150 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement with respect to the genus of methods comprising the use of an antibody or fragment thereof that binds to a human antigen-presenting molecule/antigen complex wherein the fragment comprises the sequence of SEQ ID NO:23. The Office Action states that claim 150 has been amended such that it no longer reads on the elected invention, however, new claim 199 has been added in place of claim 150. The Office Action states that those of skill in the art would have expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation are required in order to produce a protein having the specified antigen-binding function; and that the present claim reads on embodiments wherein the CDRs may be in any order, and wherein each CDR may be present in either the heavy or light variable chain. The Office Action's rejections are respectfully traversed.

Claim 150 has been withdrawn but is currently amended such that the CDRs in their proper order (*i.e.*, CDR1, CDR2 and CDR3) and context of the heavy/light chains are claimed as well as in the context of the framework sequences. Withdrawn claims 200-211 have been amended accordingly. Support for the amendments can be found in Page 56, line 18, and Table 3 in Pages 72-73 of the instant application as filed.

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Claim 199 has been amended herewith such that the CDRs in their proper order (*i.e.*, CDR1, CDR2 and CDR3) and context of the heavy/light chains are claimed as well as in the context of the framework sequences. Support for the amendments can be found in Page 56, line 18, and Table 3 in Pages 72-73 of the instant application as filed.

The Office Action has further rejected claims 141-149, 151-160 and 196-198 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Office Action states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Specifically, the Office Action states that the claims have been amended to read on methods of using any of a genus of antibodies that are described as capable of binding to a complex "composed of a human antigen-presenting molecule and an antigen" and wherein the antibody "does not bind the antigen-presenting molecule in an absence of the antigen... and the antibody does not bind the antigen derived from the pathogen in an absence of the human antigen-presenting molecule" and are rejected as exceeding the scope for which adequate descriptive support has been provided. The Office Action states that it is not clear from the teachings of the application that the identified antibodies meet the newly added functional features of the claims and there does not appear to be any screening of the identified antibodies for the inability to bind the APM or antigens other than as part of the APM/antigen complex. The Office Action's rejections are respectfully traversed.

Applicants point out that in sharp contrast to Office Action's assertion the instant application provides sufficient written description and reduction to practice, e.g., reduction to drawings and description of experimental results which satisfies the written description requirement for the claimed method. Thus, antibodies which were isolated based on their binding to a specific APM/antigen complex (e.g., the Fabs T3D4, T3E3, T3F2) were qualified for their ability to bind the target APM/antigen complex (e.g., the HLA-A2/Tax_{11-19} antigenic peptide) but not the APM when

complexed with control antigenic peptides [*i.e.*, human antigen-presenting molecule in an absence of the antigen derived from the pathogen, as claimed e.g., the HLA-A2 restricted peptides derived from HIV, CMV, hTERT, Gp100, MUC-1 or MART, see e.g., Figures 3a-c; Page 15, lines 6-8, Page 74, lines 11-25, in the instant application as filed], or the antigenic peptide (e.g., Tax_{11-19}) alone, *i.e.*, does not bind the antigen derived from the pathogen in an absence of the human antigen-presenting molecule. See Page 74, lines 26-28 in the instant application as filed. The claimed functional features of the antibodies were further confirmed in experiments utilizing cells presenting the APM/antigen complex. Thus, the antibodies were shown capable of binding cells expressing the APM molecule which were loaded with the specific peptide (thus enabling the formation of the APM/antigen complex within the cell), but not the same cells when loaded with control antigenic peptides (*i.e.*, the antibodies did not bind the APM when not in complex with the specific antigenic peptide; See Figures 5a-f, Page 15, lines 18-27; Page 75, lines 8-33 and Page 76, lines 1-2 in the instant application as filed). In addition, the antibodies were shown capable of specifically binding cells expressing the APM which were transfected with an expression vector encoding the antigenic peptide (TAX) but not cells which do not express the APM but which were transfected with the same TAX expression vector [*i.e.*, the antibodies did not bind the antigenic peptide in the absence of the APM; see Figures 7a-b, Pages 16 (lines 3-16), 76 (lines 26-33), 77 (lines 1-2) in the instant application as filed]. Thus, in contrast to Office Action's assertion, it is clear from the specification that due to their screening process (which includes testing their ability to bind the APM/antigen complex but not to the APM or antigen when not in complex) the isolated antibodies of the claimed invention meet the newly added functional features. Thus, it is Applicants' position that the instant application complies with the written description requirement since it combines both structural and functional language, *i.e.*, antigen binding domain and specific target (complex and not its constituents).

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The Office Action cites *In re Smyth* and states that the presence of multiple species within a claimed genus does not necessarily demonstrate possession of the genus ("where there is unpredictability in performance of certain species...).

Applicants further point out that *In re Smyth* is not relevant because the instant application discloses the experimental conditions by which the antibodies can be reproducibly generated *i.e.*, by screening antibody's libraries with the APM/antigen complex and qualifying the isolated antibodies for their ability to bind the APM/antigen complex but not the APM or the antigen when not in the complex. Thus, since the method of obtaining the APM/antigen complex is disclosed and the experimental conditions for obtaining antibodies capable of binding the complex are disclosed, the antibodies can be routinely obtained (no unpredictability). In the absence of adequate reasons advanced by the Office Action to establish lack of predictability, Applicants submit that this rejection is improper.

The Office Action further states that the application discloses the CDR sequences of 14 different antibodies according to the present claims, however, each of the antibodies is directed to a single APM/antigen complex, the complex comprising a recombinant HLA-A2 MHC, beta2-microglobulin and a specific HTLV-1 Tax peptide, and no antibodies binding to any other such complexes have been disclosed.

In response, Applicants point out that the application provides sufficient written description for methods of killing target human cells displaying a specific complex composed of an APM and an antigen derived from a pathogen. Applicants refer the Examiner to reduction to practice in killing human cells using an antibody directed against the HLA-A2:Tax_{11-19} complex (Figure 10, description on Page 17, lines 16-25; Page 81, lines 12-15) as well as to the description of additional antibodies directed against other APM/antigen complexes which can be used for killing target human cells as claimed (see Pages 37-40 in the instant application as filed). For example, the application describes complexes formed of APM molecules such as MHC class II molecules (e.g., HLA-DP, HLA-DQ or HLA-DR), CD1 molecules (e.g., CD1a, CD1b, CD1c or CD1d) or MHC class I molecules (e.g., HLA-A such as HLA-A2 or HLA-A2.1, HLA-B, or HLA-C molecule) with specific antigens such as those

derived from non-intracellular pathogens, intracellular pathogens or antigens which specifically associate with CD1 molecules. In addition, Applicants point out that as described hereinabove with respect to the 112 first paragraph enablement rejections (see Table 1, hereinabove and the attached Declaration by Dr. Yoram Reiter), the method of obtaining antibodies directed against specific APM/antigen complexes as disclosed in the instant application enabled the isolation of multiple antibodies directed against other APM/antigen complexes, which were encompassed by the scope of the claims and for which written description was provided (See Table 1, hereinabove). Thus, it is Applicants' position that the application fulfills the written description requirement for the genus of antibodies capable of binding a complex of APM and an antigen.

The Office Action further states that although the Office generally accepts that disclosure of the target antigen is sufficient descriptive support for a genus of antibodies binding such (MPEP 2163 II.A.3(a); and *Noelle v. Lederman*), the facts of the present case vary from those indicated in the MPEP and in Noelle in two aspects: (1) the present claims are not merely directed to an antibody that binds to the indicated antigen but require the additional functional features and (2) Applicants have presented evidence that the mere provision of the complex is not alone sufficient to obtain the antibodies described in the present claims (Declarations by Cerundolo and DeLisi).

Applicants clarify that the added functional features merely point out the specificity of the antibodies for better distinguishing the claimed antibodies from antibodies which recognize the APM or peptide alone (*i.e.,* when not in complex). The claimed functional features are well accepted for defining the specificity of the antibodies. Applicants point out that the USPTO have issued numerous patents which comform with the pending claimed language see e.g., U.S. Patent No. 5,985,579 which claims an antibody with functional features as follows:

"28. A test device for performing an assay to determine the presence or amount of at least one target ligand in a fluid sample suspected of containing said

target ligand, said target ligand capable of binding to a ligand receptor conjugate and to an antibody immobilized to a surface of the device, said device further comprising:

a. a means for contacting said fluid sample with said ligand receptor conjugate and the immobilized antibody, said antibody capable of binding the complex of said target ligand and said ligand receptor conjugate, the binding affinity of said antibody for said complex being at least a factor of 10 greater than the affinity of said antibody for said target ligand, wherein no detectable assay response results from the binding of antibody and ligand receptor conjugate in the absence of target ligand, wherein the amount of ligand receptor conjugate bound to antibody is related to the amount of target ligand in the fluid sample;

b. a means for detecting said complex bound to said antibody; and,

c. a means for relating the presence or amount of complex detected to the presence or amount of said target ligand in said fluid sample, wherein said device is adapted and arranged such that the assay, when performed, is essentially unaffected by a hook effect.

(Emphasis added).

Similarly, see for example the claims of U.S. Patent Nos. 7,244,429, 6,703,489, 6,858,706, 4,851,334, 6,653,084 and 6,538,113.

Applicants point out that in contrast to Office Action's assertion and as mentioned hereinabove, screening for antibodies with the required functional features is fully disclosed and supported by the application. In addition, with respect to the Declarations by DeLisi and Cerundolo and as mentioned above, the lack of success in isolating the TCR-like antibodies was when using the prior art methods and not the method disclosed in the instant application (see Declaration by Cerundolo, Pages 2-4; Declaration DeLisi, Pages 2-4).

In fact, as mentioned hereinabove and stated in the attached declaration, using the teachings of the instant application antibodies capable of binding the APM/antigen complex are routinely obtained at high frequencies for every target APM/antigen complex attempted.

The Office Action states that the application discloses a method for the production of the antibodies used in the claimed methods however, the Court of Appeals has indicated that the provision of such a method does not provide adequate descriptive support for compounds that may be identified through its use (*University of Rochester v. G.D. Searle & Co*).

Applicants' position is that the Office Action is overreaching in citing this case law. In fact in this case the trial judge found that although all claims required use of a non-steroidal compound, the specification did not disclose the compound, provide means of identifying the compound other than trial and error or even indicate that the university knew of such a compound.

This is certainly not relevant to the present case since examples of the claimed antibodies are disclosed in Pages 71-77, including Table 3, means for identifying same are described at length in Pages 14-16 and 64-77 in the instant application and additional antibodies were thus reproduced (see attached Declaration by Dr. Yoram Reiter).

Thus, it is Applicants' position that the instant application provides sufficient written description since it describes a novel and efficient method which is highly reproducible (see attached Declaration by Dr. Yoram Reiter).

In view of the above claim amendments, arguments and remarks Applicants believe to have overcome the 35 U.S.C. §112, first paragraph rejections.

Double Patenting

Claims 141-160 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48-50 of co-pending Application No. 11/203,137, or the co-pending claims in view of the teachings of Reiter and Andersen in view of Hoogenboom, Matsushita or Saito. Applicants request that these rejections be held in abeyance until there is an indication of allowability in at least one of the cases.

In addition, claims 141-160 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8 and 11 of copending Application No. 11/629,194, or the co-pending claims in view of the teachings of Reiter and Andersen and Hoogenboom. Applicants request that these rejections be held in abeyance until there is an indication of allowability in at least one of the cases.

In view of the foregoing amendments and remarks, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested. A prompt Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,

Martin D. Moynihan
Registration No. 40,338

Date: April 9, 2008

Enclosures:

- Request for Continued Examination (RCE);
- Petition for Extension of Time (3 Months);
- Signed Declaration by inventor Dr. Yoram REITER;
- Appendix; and
- Yoram REITER's Curriculum Vitae